Remarks/Arguments

Claims 1, 2, 4-16, 26-34 and 36-38 are pending in the application. Claims 17-25 have been canceled. Claims 26-34 and 36-38 have been withdrawn from consideration pursuant to a restriction requirement.

Claim 1 has been amended. Support for the amendment is found in claim 3, which has been canceled. Minor editorial amendments have been made to claim 4 and 5.

Information Disclosure Statement

Gray *et al.*, Biological Abstracts no. 272061, was not considered because it was not received by Examiner. A copy of that reference is enclosed with a further PTO Form 1449. Consideration of the Gray *et al.* reference is respectfully requested. Examiner is requested to initial and return one copy of the Form 1449 to the undersigned.

Response to Section 103 Rejections

Claims 1, 2, 6-9, 13-18 and 22-25 are rejected as being unpatentable over Staples *et al.* in view of WO /9522258. Claims 1, 3-6, 10-12, 17 and 19-21 are rejected as being unpatentable over Staples *et al.* in view of WO /9522258, further in view of WO 96/02571. Claims 3 and 17-25 have been cancelled herein. Reconsideration of the rejection of claims 1, 2, and 4-15 is respectfully requested in view of the following remarks.

The inventiveness of the present application is based upon the fact that it is generally accepted that the pH of the medium in which cation ion exchange chromatography (CEX) separation is carried out is usually below the isoelectric point of the protein to be bound. The isoelectric point or pI of the protein is the pH value at which the protein carries no net charge. At pH values above the pI, the protein has a negative charge and at pH values below the pI the protein has a net positive charge and will bind the CEX substrate (as described on page 9, line 23, to page 10, line 1, of the present application). The inventors surprisingly found that fibrinogen can be bound to CEX substrate at pH values above the reported pI of the protein directly from milk and that this attribute could be used to develop a very effective purification technique (page 11, lines 14-16, and page 12, lines 13-19). This

feature of the invention is recited in claim 1, as amended. The pI of fibrinogen is understood to be pH 5.5 as recited on page 16, lines 13-15. The present invention uses CEX at a pH greater than 5.5 and preferably around pH 6 (page 16, line 20).

Staples *et al.* describes the partial purification of a recombinant soluble T4 protein (rsT4). rsT4 is a highly basic protein as recited in column 6, lines 66-67 of Staples and is therefore a suitable candidate for CEX purification. The Examiner's argument is based upon the fact that Staples *et al.* uses a pH 8.5 solution (column 6, lines 41 to 46 and line 58). In this respect the Examiner is only partially correct. Staples *et al* uses a pH 8.5 buffer to elute the bound protein from the CEX column rather than using it as the binding buffer. By raising the pH the rsT4 is eluted from the column rather than bound to it. Consequently such a high pH solution buffer is inappropriate for binding of rsT4 to the CEX column. In fact the binding of this highly basic protein is at pH 5.5 (column 6, lines 34 to 37). Consequently the successful binding of rsT4 does not take place at a pH higher than its pI. The rsT4 molecule is a highly basic protein and consequently it must have a pI of above 7. Thus Staples *et al.* does not teach the same inventive principle as the present application, i.e., the binding of a protein of interest (in this case transgenic fibrinogen) at a pH greater than its pI.

The deficiencies of Staples *et al.* are not remedied by WO 95/22258. The latter teaches a method for obtaining lactoferrin from milk. It is known that lactoferrin has an isoelectric point of 9.7. As a highly basic protein it is therefore a suitable candidate for CEX purification. Again there is no teaching that lactoferrin is bound at a pH higher than its pI. In fact on page 18, line 18, the pH of the buffer is stated to be pH 7, which is below lactoferrin's isoelectric point. Consequently WO 95/22258 does not teach the same inventive principle as the present application, i.e., that binding of transgenic fibrinogen occurs at a pH greater than its isoelectric point and that this surprising observation can be used to purify transgenic fibrinogen effectively from milk.

It is respectfully submitted that the invention of claims , 1, 2, 6-9 and 13-15 would not have been obvious to one of ordinary skill in the art from the combination of Staples and WO 95/22258.

While WO 96/02571 does not remedy the deficiencies of Staples *et al.* or WO 95/22258. While WO 96/02571 mention the use of ion exchange chromatography at column 4, lines 57-59, it does not mention the pH conditions. The disclosed method is based on precipitation at acid pH as recited at column 3, lines 34-36, and not chromatography. Thus, the invention of claims 1, 4-6, and 10-12 would not have been obvious to one of ordinary skill in the art from the Staples *et al.* and WO 95/22258, even if further combined with WO 96/02571.

Accordingly the applicant submits that the present invention is not obvious when viewed either in the light of Staples *et al.* and WO 95/22258, or when viewed in light of Staples *et al.*, WO 95/22258 and WO 96/02571.

The claims remaining in the application are believed in condition for allowance. An early action to that end is earnestly solicited.

Respectfully submitted,

GRAHAM MCCREATH

BY _____

DANIEL A. MONACO
Registration No. 30,480
DRINKER, BIDDLE & REATH, LLP.
One Logan Square, 18th and Cherry Streets
Philadelphia, PA 19103
Tel. (215) 988-3312
Fax (215) 988-2757
Attorney for Applicant